Summary of Findings of COVAX R&D and Manufacturing Investment Review

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Background and introduction

COVAX R&D portfolio governance

The Research & Development and Manufacturing Investment Committee (RDMIC) is a multidisciplinary group with industry expertise that manages the allocations of funds under the Development and Manufacturing Workstream of COVAX. It provides investment decision recommendations for selection and progression of the portfolio of COVAX-funded vaccine candidate projects and cross-cutting enabling projects that accelerate vaccine R&D and manufacturing.

The RDMIC reports to the COVAX Coordination Meeting (CCM). RDMIC operates as an expert advisory group to the lead COVAX institutions (CEPI, Gavi and WHO), who remain accountable to their respective institutional governance and investor requirements for ultimate COVID-19 R&D and manufacturing portfolio investment decision-making. Any decisions are deemed to be for a given lead institution only, as opposed to relating to COVAX, are made through the respective institutional governance structures. The majority of COVAX' R&D and manufacturing investments are ultimately funded by CEPI, therefore the majority of RDMIC's recommendations are actioned through CEPI's institutional investment governance.

The RDMIC provides portfolio strategy and investment decision recommendations to rapidly identify, develop and manufacture COVID-19 vaccines that can be deployed at scale to address global health needs. To that end, the RDMIC defines the target composition, diversity, investment allocation and risk profile of the portfolio of COVAX-funded vaccine candidate projects and cross-cutting enabling projects. It also provides overall oversight of project progress and serves to endorse new projects; provide resolution of significant project issues escalated by the Technology Review Group (TRG); and endorse recommendations for project progression through stage gates provided by the TRG.

The principal objectives of the RDMIC are:

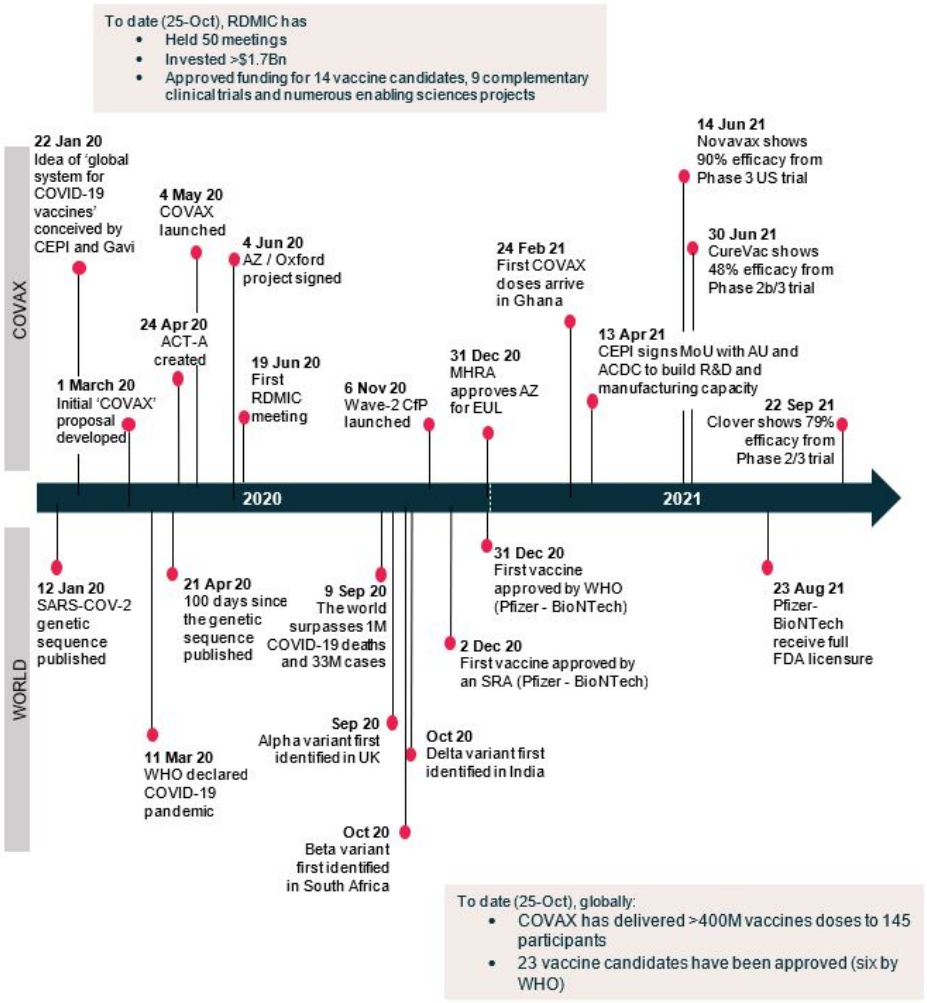
1. Drive portfolio strategy and investment decision recommendations aligned with overall COVAX strategic objectives
2. Define the target composition, diversity, investment allocation and risk profile of the portfolio of COVAX-funded vaccine candidate projects and cross-cutting enabling projects
3. Recommend project selection and investment decisions >$5M
4. Oversee overall progress of the COVAX-funded vaccine candidate projects and cross-cutting enabling projects
5. Identify and address cross-portfolio challenges and interdependencies

Purpose and objectives of the review

RDMIC was established in June 2020 and has met on an approximately weekly basis. A review of RDMIC's activities during the COVID-19 pandemic has been conducted to capture learnings relating to the impact and effectiveness of RDMIC's investment decisions in the context of the COVID-19 pandemic. The outcome of this exercise will help inform:

- Ongoing focus and scope of the RDMIC in the current pandemic
- Future global pandemic response efforts, particularly related to R&D investments
- Best portfolio governance practices for incorporation into CEPI's core (non-COVID-19) portfolio governance activities.

Timeline of key events and milestones



Methodology

Interviews with 11 RDMIC members were conducted between 27 July and 16 September 2021. Findings from these interviews have been synthesised and an independent review of the key findings has been compiled by Amanda Glassman (Centre for Global Development).

Interviewees:

- Chris Viehbacher, RDMIC Chair (Gurnet Point Capital)
- Seth Berkley (Gavi)
- Richard Hatchett (CEPI)
- Subhash Kapre (Inventprise)
- Michael King (Independent Consultant, retired Merck/MSD)
- Kiran Mazumdar-Shaw (Biocon)
- Trevor Mundel (Bill & Melinda Gates Foundation)
- Peter Paradiso (Independent Consultant)
- Melanie Saville, Technical Review Group Chair (CEPI)
- Luc Debruyne, Strategic Advisor (CEPI)
- Marie-Paule Kieny (COVAX Independent Product Group)

Key findings

1. Portfolio diversification and risk management:

The RDMIC's recommendations to invest in a broad set of vaccine technologies/platforms and inputs across a range of developers and manufacturers, led to the development and production of many high-efficacy vaccines, including vaccines manufactured in geographically diversified sites.

- The COVAX R&D portfolio was highly diversified, and many candidates were ultimately efficacious. RDMIC did "*a credible job of building a portfolio with the funding available.*" RDMIC was "*effective in allocating funds to create a portfolio of companies, geographies and mechanisms of action designed to minimize the risk that arose when/if the world's largest global vaccine manufactures did not succeed in rapidly developing a COVID vaccine.*"
- Multiple private vaccine manufacturers were able to develop and manufacture significant quantities of vaccine in a historically short period of time. RDMIC investment recommendations played a role; serving as a mechanism to match funding with projects in view of significant uncertainty about novel platform technologies, mechanisms of action and capabilities of different companies. "*Active management of the portfolio was the big accomplishment.*" "*Backed mRNA very early though CureVac and Moderna.*"
- The RDMIC was effective at identifying and mitigating risks on an ongoing basis as projects progressed: the committee identified at an early stage the technical challenges that some of the portfolio developers were likely to experience in technology transfers, and recommended that creation of a

dedicated team to work directly with developers to manage these risks; the committee also recognised the need to secure and centrally manage supplies of adjuvant and materials (e.g. medical glass) to enable allocation across the portfolio on the basis of highest priority.

- CEPI was able to raise and deploy public and philanthropic monies to allow companies to take significant risk by advancing various stages of vaccine development at once.
- But: despite the mandate, funding was entirely inadequate given the scale of the challenge and, too often and closely connected to inadequacy of funding, investment decisions were made in a risk-reducing sequential approach rather than a simultaneous end-to-end approach.
- Furthermore, once efficacy had been demonstrated by the leading vaccine candidates in the field, RDMIC might have taken steps to narrow the focus of investments earlier. "*Did RDMIC keep a broad portfolio in place for too long, when "winners" were clear? What were the opportunity costs of staying broad?*"
- Another area that could have benefitted from greater focus was geographic diversity of investments – for example the COVAX R&D portfolio did not include investment in any of the inactivated vaccines developed in China, where the speed to vaccine – even with relatively low efficacy – might have been important to limit spread.

While RDMIC took deliberate steps to identify and characterise the different risks within the COVAX R&D portfolio, more could have been done to mitigate regulatory and manufacturing risks, particularly where developers or manufacturers were inexperienced.

- "*Regulatory risks needed more attention – consider a mechanism for coordination on CMC issues that affect the efficiency of trials and the efficiency of their regulatory review, for example, harmonization of endpoints, single assay for antibodies, etc."*
- CEPI did not enter the pandemic with major capabilities in either regulatory or CMC. CEPI's investors initially conceptualized the organization as only developing vaccine up to Phase II, assuming that the private sector would come in after that. RDMIC brought experience and expertise in some of these areas, but more intentionality was needed. CEPI has strong expertise in clinical development, however the pandemic identified a need to build out capabilities in manufacturing and regulatory matters, the latter beyond the remit of WHO.
- Related to the above, the RDMIC agenda was "*focused mainly on product development and less on supply*"; "*more focus on clinical development of the vaccines than a focus on the end-to-end process*". This approach was understandable given the uncertainty about which vaccines would work but suggests a need for an end-to-end approach in the future. "*There is a need to support large-scale manufacturing up to regulatory approval.*"
- Related to these risks, there was limited RDMIC visibility into the agreements governing the programs (between CEPI and development partners for R&D funding; and between Gavi and manufacturers for vaccine procurement), and not always full clarity on the rights of CEPI vis-à-vis grantees. These rights and insights could potentially have been strengthened by more intentionally structuring R&D push funding together with regulatory/manufacturing support and advance purchase agreements to enable greater leverage with portfolio companies.

- "*COVAX fell down as a market mechanism*" – the Facility had some seed funding but there was no clear market opportunity for commercial developers, in contrast to Operation Warp Speed (OWS) for example. Therefore, the influence of RDMIC – and COVAX in general – over portfolio companies was weaker.
    - Lack of at-risk funding affected decision-making and its timing, as well as the content of the portfolio itself; ultimately none of the major global vaccine developers were incentivised to offer supply to COVAX in return for R&D investment.
    - There may have been opportunities to better align and achieve synergies with OWS processes to compete with high-income countries who pursued bilateral arrangements for supply directly with manufacturers.
- Other actions that could have been taken to mitigate risks:
- Consideration of worst-case scenarios as a matter of routine: More monitoring of inputs and supply chain challenges
- More proactive challenge and management of expectations in view of unrealistically ambitious development and supply forecasts, particularly by non-established vaccine producers
- Having more fleshed-out alternative strategies to respond and adapt to the impact of geopolitical issues on COVAX supply, such as bilateral arrangements between governments and manufacturers, and export restrictions imposed by countries in the COVAX supply chain.

2. COVAX governance and oversight; and remit of RDMIC

COVAX is not a legal entity and therefore lacks both i) a unified and agile command and control structure to operate in crisis response mode, and ii) a one-stop shop for R&D, manufacturing, procurement and distribution. Delegated authority across different institutional partners also differed, frequently presenting a barrier to rapid decision making.

While RDMIC understood its role in providing investment oversight for the COVAX R&D portfolio – as distinct from the COVAX Facility (procurement) portfolio – given the overarching COVAX objective of securing two billion doses of safe, effective vaccine by end 2021, RDMIC frequently considered issues across the R&D portfolio in view of the potential impact on downstream procurement. However, the COVAX Facility also had separate scientific and technical advisory group (the Independent Product Group) to ensure objectivity in procurement decisions – which at times created additional bureaucracy.

In addition to the very limited funding available, each organization had a different mandate and risk appetite. If adequate financing had been available earlier, the overall end to end risk tolerance may have been more aligned.

Greater geographical diversity in membership was highlighted as an area for future attention. While a representative from the Africa CDC was a standing member of the Committee, there was no active involvement from representatives from Latin America or Asia. From a functional perspective, greater regulatory expertise was highlighted as an area to address, along with greater epidemiology expertise.

3. Need for R&D and Manufacturing investments in the current pandemic

For the current pandemic, the priority is to execute on the existing agenda. While there were some divergent perspectives, most recommended near-term focus on:

- Developing better versions of existing vaccines (e.g., addressing thermostability, lower cost, easier to produce and/or deliver)
- Defining a variant strategy (boosters v new vaccine designed for variants)
- Developing manufacturing capacities and addressing manufacturing bottlenecks
    - Investing in a network of suppliers over the next year, let each know what it would take to gain support; relate to current dialogue on creation of regional hubs
    - Continue work to de-bottleneck supplies and constraints to near-term LMIC supply and delivery
    - Partner to develop mRNA manufacturing platforms in different geographic areas but consider that mRNA requires certain inputs (e.g., enzymes) for which there are on-going shortages. Consider curation of mRNA libraries in the longer term

Note: there is a need to clarify CEPI's role in supporting manufacturing, distinguishing from other entities and sources of support. However, RDMIC's strong technical expertise in this area could be mobilized to select manufacturing investments more strategically and with an eye to impact and access in LMICs.

4. R&D and Manufacturing priorities for future pandemics

To enhance R&D and manufacturing investment decision making for future pandemics, it will be important to combine lessons learned from COVAX together with experiences from OWS. An example is the need to link up R&D funding with regulatory, manufacturing and supply chain investments, bundling together for insight and leverage with portfolio companies to meet access goals given the need for rapid response. Ideas shared include:

- Build callable capital facilities that can be deployed when a pandemic-potential outbreak hits, agree on structure and governance of uses ex ante, etc.
- Fund manufacturing innovation, new manufacturing technologies: global system/network; scalable plants; process intensification; repurposed capacity
- If a global mechanism is mobilised in the future (a successor to COVAX), the investment in R&D has to be coupled with procurement / advance purchase agreements
- Consider whether CEPI could become a one-stop shop in the future, including early procurement OR whether CEPI should be the articulating point around which regional entities such as BARDA and HERA – with analogous entities being stood up to cover other geographic regions – operate, with CEPI playing a global networking, coordinating and advisory role
- Future funding of vaccines should target vaccines against multiple major respiratory pathogens; pancoronavirus vaccine (already under discussion).